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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,800	03/13/2001	Joseph Sypek	GNN-018CP	2859

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/24/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/805800	SYPEK
Examiner	**Art Unit**
GAMBEL	1644

Office Action Summary

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/18/04

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) ____ is/are pending in the application. 1-13

4a) Of the above claim(s) ____ is/are withdrawn from consideration. 4

5)☐ Claim(s) ____ is/are allowed.

6)☑ Claim(s) ____ is/are rejected. 1, 2, 4-13

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on ____ is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on ____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4)☐ Interview Summary (PTO-413) Paper No(s). ____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 9

DETAILED ACTION

1. Applicant's election of the species (C) B7-1- and B7-2-specific antibodies, of the species (B) in vivo and of the species systemic lupus erythematosus in Paper No. 5, filed 7/18/02, has been acknowledged.

Claims 1, 2 and 4-13 are under consideration in the instant application.

Claim 3 has been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected species.

2. The filing date of the instant claims appears to be the filing date of priority application USSN 60//189,106, filed 3/14/00..

3. Formal drawings, filed 11/18/02, comply with 37 CFR 1.84.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is reminded that the following and should amend the specification (e.g. see page 25) accordingly. The current address of the ATCC is as follows:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

Appropriate corrections are required

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. It is noted that the elected invention is drawn to targeting "B7-1" and "B7-2", wherein there is sufficient written description and enablement. However, in the interest of compact prosecution, applicant is invited to amend the claimed limitations of "B7 molecule" to those disclosed in the specification as filed (e.g., see page 6, paragraph 2 and pages 11-12, overlapping paragraph).

7. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1, 2 and 4-13 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing "a B7 molecule(s)" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the genus of "B7 molecules" are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

For example, page 6, paragraph 2 and pages 11-12, overlapping paragraph of the instant specification discloses certain known B7 molecules, including B7-1, B7-2, B7RP-1 and B7h.

Applicant is relying upon certain biological activities and the disclosure of this limited representative number of species to support an entire genus. The instant invention encompasses targeting any "B7 molecule(s)" to inhibit immune responses, including the treatment of SLE, yet the instant specification does not provide sufficient written description as to the structural features of said "B7 molecule(s)", as currently encompassed by the claims. Also, the specification does not provide for the correlation between the chemical structure and the function of the genus of "B7 molecules", currently encompassed by the claimed invention. The reliance on the disclosed limited examples of certain known "B7 molecules" indicated above and disclosed in the specification as filed does not support the written description of any "B7 molecule". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. The specification as filed does not provide written description for B7 molecules structurally unrelated to the limited genus of "B7 molecules" indicated above and disclosed in the specification as filed and encompassed by the claimed invention.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a "B7 molecule" indicated above and disclosed in the specification as filed

There is insufficient guidance based on the reliance on the "B7 molecule" indicated above and disclosed in the specification as filed to direct a person of skill in the art to select or to predict particular sequences as essential for identifying any "B7 molecule" nor what other "B7 molecule(s)" are targeted in the claimed methods, as encompassed by the claimed invention.

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "B7 molecules", the specification does not provide sufficient written description for the genus of "B7 molecules" targeted by the current claims.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "B7 molecule(s) targeted in the claimed methods to downregulate immune responses; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

8. Claims 1, 2 and 4-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain known B7 molecules, including B7-1, B7-2, B7RP-1 and B7h disclosed on page 6, paragraph 2 and pages 11-12, overlapping paragraph of the instant specification, does not reasonably provide enablement for any "B7 molecule(s)" to be the specificity targeted in the claimed methods to downregulate the immune responses.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. molecule

Again, page 6, paragraph 2 and pages 11-12, overlapping paragraph of the instant specification discloses certain known B7 molecules, including B7-1, B7-2, B7RP-1 and B7h.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any "B7 molecule" as the target specificity of the claimed methods. "B7 molecule(s)" may have some notion of the function of the cell surface receptor, however, claiming biochemical molecules by a particular name given to the protein (e.g., B7 molecule(s)) by various workers in the field fails to distinctly claim what that protein is and what it is made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "B7 molecule(s)".

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Applicant is relying upon certain biological activities and the disclosure of this limited representative number of species to support an entire genus. The instant invention encompasses targeting any "B7 molecule(s)" to inhibit immune responses, including the treatment of SLE, yet the instant specification does not provide sufficient guidance and direction how to make and use any "B7 molecule", as currently encompassed by the claims. Also, the specification does not provide for the correlation between the chemical structure and the function of the genus of "B7 molecules", currently encompassed by the claimed invention. The reliance on the disclosed limited examples of certain known "B7 molecules" indicated above and disclosed in the specification as filed does not provide sufficient enablement of any "B7 molecule". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. The specification as filed does not provide sufficient enablement for B7 molecules structurally unrelated to the limited genus of "B7 molecules" indicated above and disclosed in the specification as filed and encompassed by the claimed invention.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "B7 molecules" other than those disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "B7 molecules" targeted by the claimed methods to downregulate immune responses.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "B7 molecule(s)" other than those disclosed in the specification as filed as the target specificity in the claimed methods

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using "B7 molecule(s)" other than the "B7 molecule(s)" disclosed in the specification as filed as the target specificity in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 2 and 4-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Co et al. (US 2002/0176855 A1) in view of de Boer et al. (U.S. Patent No. 5,5,747,034), Cottens et al. (WO 95/16691)(1449; #A12) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456).

Co et al. teach methods of inhibiting B7:CD28/CTLA-4 pathway, including treating autoimmune diseases such as SLE (e.g., see page 10, column 1, paragraph 4; with B7-specific antibodies, including the combination of anti-B7-1 and anti-B7-2 antibodies with other standard therapy drugs such as methotrexate, cyclosporin and steroids (page 10, columns 1-2, overlapping paragraph) (see entire documents, including Detailed Description of the Invention, particularly Therapeutic Methods and Compositions). Co et al. teach known modes of administration and pharmaceutical compositions which can be administered in a single dose or in more than one dose over a period of time to confer the desired effect, which is based on a particular patient as determined by one of ordinary skill in the art (see page 11, columns 1-2). See entire document.

Co et al. differs from the claimed invention by not teaching the known use of rapamycin in the treatment of SLE at the time the invention was made.

De Boer teach the use of anti-B7 antibodies which can be given in combination with one or more immunosuppressive agents, including immunosuppressive agents which block or inhibit the activation or proliferation of T cells, including rapamycin (see columns 14, Immunosuppressive Agents). De Boer et al. teach the use of anti-B7 antibodies to treat various diseases and conditions, including SLE (column 15, paragraph 1). Here, too, the dosage and mode of administration will depend on the individual (see column 15-16, formulation and Methods of Administration). See entire document.

Cottens et al. teach the use of rapamycin as an immunosuppressant for various inflammatory conditions, including SLE (see entire document, including page 9, The Novel Compounds are particularly useful for the following conditions, particularly Section (b)). Cottens et al. teach the administration of rapamycin together with other immunosuppressives for treatment, including in combination with other immunosuppressive monoclonal antibodies (see page 11, paragraph 4). Consistent with the other teachings and general practice at the time the invention was made, the modes of administration and dosages will depend on the condition to be treated (e.g. the disease type or nature of resistance) for the subject in need (see page 11, paragraph 1-3). See entire document.

In further evidence, the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456). These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway, including the expectation of achieving additive-synergistic effects (e.g. see page 451 and Figure 36.1). A basic principle includes the appropriate reduction or withdrawal of an immunosuppressive drug when that drug's toxicity exceeds its therapeutic benefit (page 451, column 2, lines 1-4). Strom et al. concludes that more refined immunosuppressive regimens including targeted discrete steps in antigen recognition, signal transduction and effector immunity are anticipated in clinical application (see page 455, column 2, paragraph 2).

Given the clear teachings of the prior art to combine anti-B7-1 and anti-B7-2 antibodies alone or in combination with other immunosuppressive therapy to inhibit immune responses, including in therapeutic regimens of treating SLE alone in conjunction with the known use of rapamycin to treat SLE alone or in combination with other immunosuppressive antibodies, including anti-B7 antibodies; one of ordinary skill in the art at the time the invention was made would have been motivated to combine anti-B7-1 and anti-B7-2 antibodies with rapamycin to inhibit immune responses in various therapeutic regimens including the treatment of SLE at the time the invention was made. The various dosing regimens encompassed by the instant claims were obvious at the time the invention was made, given that it was well known and practice at the time the invention was made to provide immunosuppressive therapy based upon the condition and needs of the patient, as evidenced by the teachings of the prior art. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
January 21, 2003